

Stem Cell Differentiation and the Microenvironment



Overview

Students will learn about stem cell differentiation (also known as specialization) into lineages, creating multiple cell types that together contribute to the development, function, and maintenance of organs and body systems. A stem cell's microenvironment contributes to its differentiation path. Depending on your students' capabilities, choose appropriate components of the microenvironment—soluble factors, cell-cell interactions, extracellular matrix proteins, and physical forces—to focus on in class and let that guide the choice of homework readings. This lesson addresses the **Next Generation Science Standards (NGSS) Performance Expectation HS-LS1-4**. View the standards that apply to this unit.

As a class, students view animations to learn about how the microenvironment contributes to the differentiation of adult stem cells. The class can construct a simplified blood cell lineage “tree” and then individually research disorders caused by abnormal blood cells. The original pool of blood stem cells and the entire blood lineage is maintained by a specialized type of mitosis called **asymmetric cell division**. Students will learn to distinguish stem cells from **progenitor cells** and that the **microenvironment** controls cell behavior.

Important Terminology

Microenvironment: the local surroundings of a cell that feed into its behavior.

Students can think of the microenvironment as the dorm/apartment in which a stem cell lives and functions. The microenvironment has non-living materials (concrete, rebar, furniture), other cells (roommates, neighbors, and visitors), as well as signaling molecules (voices, visuals, objects in the way) that help our stem cell character navigate in the world and decide what to do. For cells, even forces (sensed as physical variations in the extracellular matrix) can influence cell fate.

The specific microenvironment of stem cells is called the stem cell niche. This environment influences the development of stem cells from quiescence through stages of differentiation. Just like the ecological niche of an organism, a stem cell niche is unique to the individual or small population and guides its dynamics. The four major components of the microenvironment are soluble factors, cell-cell interactions, extra-cellular matrix proteins, and physical forces.

Soluble factors: Received from the extracellular environment, soluble factors typically bind a cell's plasma membrane or cytoplasmic

receptors. Soluble factors, such as proteins, hormones, and chemicals, vary in biochemical composition and origin.

Cell-cell interactions: Cells can also receive extracellular signals from connections made with their neighbors. These connections can vary in size, composition, strength, and cargo transported. Normal cells grown in a petri dish will divide until they completely cover the surface, when they experience contact inhibition and stop dividing. But cancer cells lose this contact inhibition, suggested by the observation that they continue growing on top of each other after they cover the whole petri dish. Cancer cells do not respond normally to growth regulatory signals induced by cell-cell interactions.

Extracellular matrix proteins: These proteins make up the scaffold within which cells adhere and grow. Extracellular matrices are made of proteins produced by connective tissue cells. They all have unique structures that contribute to both the biochemical and mechanical signaling in a given tissue. Collagen, fibronectin, and laminin are proteins that can assemble into extracellular matrices in the body and signal to cells. These proteins form a matrix that varies in stiffness due to protein density and organization. For example, brain is soft and very elastic, skin has intermediate stiffness, muscle is stiffer, and bone is very stiff and inelastic.

Forces: Cells adhered to the extracellular matrix can sense the stiffness of their surroundings by anchoring and pulling using adhesion molecules and myosin-based contraction. This pulling also generates small contractile forces that can change the organization of the extracellular matrix. Cells can respond to the stiffness they feel by reorganizing their cytoskeletons and initiating other cellular processes. They respond by changing their own stiffness—sometimes even locally reorganizing the matrix to change its stiffness, which can signal a different response from the cells!

Symmetric cell division: this is the basis of proliferation (also known as self-renewal), the expansion of a population of cells. During symmetric division, a stem cell or body cell undergoes mitosis into two daughter cells identical in cellular potential. For example, a stem cell can divide into two stem cells, and an astrocyte (a type of brain cell) can divide into two astrocytes.

Asymmetric cell division: this is the basis for differentiation, the maturation of an unspecialized cell down a defined lineage. During asymmetric division, a stem cell or a progenitor cell undergoes mitosis into two daughter cells, one of which remains a stem/progenitor cell while the other becomes a more specialized cell. For example, a neural progenitor cell can divide into two daughter cells, one remaining a neural progenitor cell and another growing into a neuron.

Progenitor cell: similar to a stem cell in that they can both differentiate into more specialized cells, however the progenitor cell is already more specific than a stem cell and is closer to its end-stage cell type. Stem cells can replicate indefinitely, while progenitor cells divide a limited number of times. The definition of a progenitor cell is still evolving.

For more information, read Teacher Background Information 3 and Teacher Background Information 4 from CIRM model stem cell curriculum Unit 3 and Unit 4.

Outline of Lesson

Discussion of Homework (do as much as time allows)

Review the following questions:

1. What is gene expression? | Transcription of a gene into mRNA and translation of mRNA into a protein.
2. What are transcription and translation? | Students can remember their order by thinking about a scroll containing ancient text. A scholar could write a transcript where she writes down the ancient language (DNA) into a modern language (RNA), say Italian. Then, a translator could translate the Italian (RNA) to English (protein) and read it to you out loud.
3. What is the difference between an embryonic stem cell and a blood stem cell? Ultimately, they have different genes being expressed, leading to a difference in the types of proteins making up the embryonic or blood stem cells. A cell is influenced by its direct environment, altering gene expression and thus its behavior. Embryonic stem cells and blood stem cells developed and reside in different environments maintaining them as stem cells that can produce multiple types of daughter cells. Embryonic and adult stem cells (like the blood stem cell) differ in the degree to which they can produce other cell types (called potential or plasticity). Embryonic stem cells can produce every cell in the body, while blood stem cells can only become the blood system. In other words, embryonic stem cells are **pluripotent** and blood stem cells are **multipotent**.

Go through the homework questions, and paint a picture that the microenvironment controls cell fate. The microenvironment even keeps a stem cell quiet or “quiescent”—neither dividing, differentiating, nor migrating. In reality, multiple factors drive cell behavior; they can be organized into extracellular events (proteins, growth factors, hormones, chemicals, oxygen levels), neighboring cells, physical environment (composition and structure of extracellular matrix proteins such as collagen), and physical forces (compression, stretching, etc.). A stem cell's microenvironment is often called a niche, parallel to an ecological niche.

View animation from Stem Cells Explained: An Interactive Tutorial (University of Michigan)
Cell Specialization

View next animation from Stem Cells Explained
Adult Stem Cells

View animation from the Riken Center for Developmental Biology
Stem Cells in the Adult Body – choose animation #3

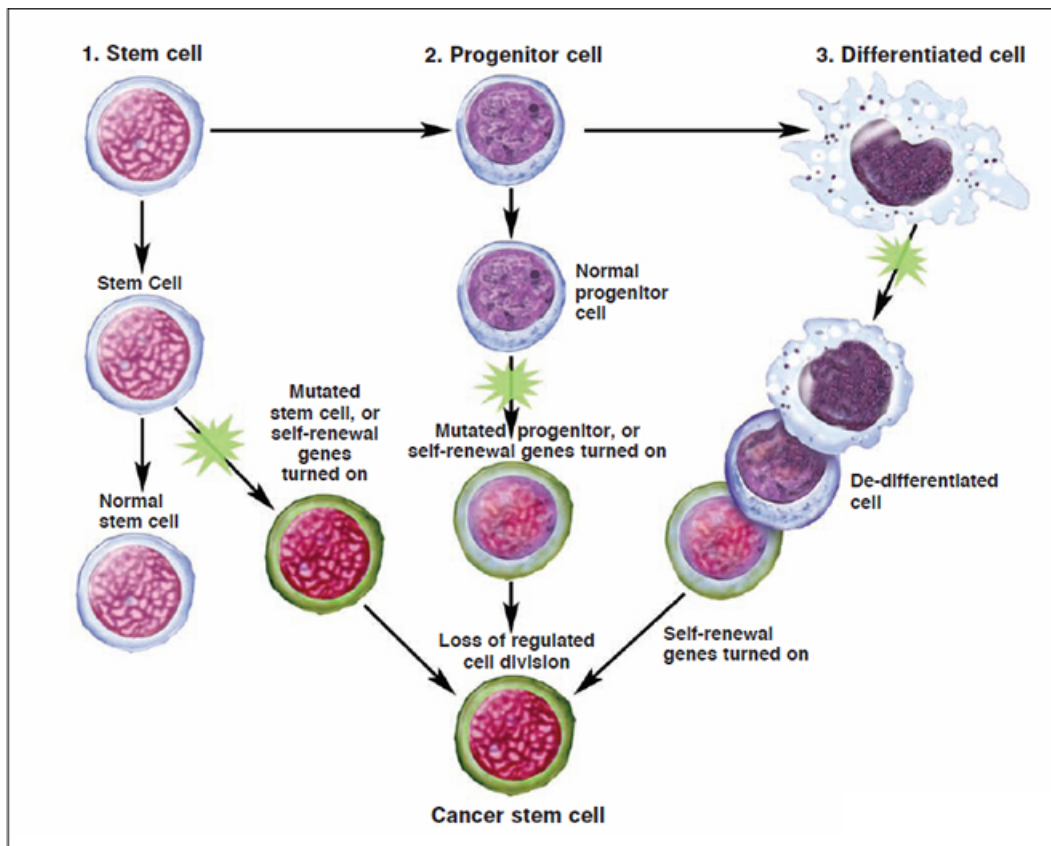
Play a game-show-like activity from Unit Four demonstrating blood stem cell potency.
"The Cell is Right" — Blood stem cell lineage tree activity

After the activity, have students research online or in the library:

1. Why are there so many types of blood cells? | This activity simplified the blood system; there are many more intermediate and end-stage types of blood cells. They each have a critical, specific function in maintaining the blood system.
2. Choose four cells within the lineage tree. Describe in detail what each one does and explain/diagram their lives from the original blood stem cell.
3. Choose one of the following: lymphoblast, red blood cell, T-lymphocyte, Natural Killer Cell. Find a disease related to that cell and explain what role that cell plays.

As a class, discuss findings. The topic of cancer should arise:

1. What is cancer? | A cell acquires gene mutations and is in a microenvironment that promotes abnormal proliferation, differentiation, and migration.
2. The Cancer Stem Cell Hypothesis reasons that mutations or self-renewal ("stemness") gene activation creates cancer stem cells from normal stem cells. Rarely, a differentiated cell can become a cancer stem cell:



Homework assignment—teacher can choose appropriate readings from the following list, organized by type of microenvironmental influence and difficulty. Students can summarize the articles in a way that integrates the components of the microenvironment: signaling factors, extracellular matrix proteins, forces, and cell-cell interactions. Cite the articles in the text as well as in a references section.

Signaling factors

1. EASY Science Daily: Key Mechanism That Regulates Development Of Stem Cells Into Neurons Identified
2. EASY Science Daily: Finnish Scientists Discover Nerve Growth Factor With Therapeutic Potential In Parkinson's Disease
3. MID Science Daily: Why Neural Stem Cells Divide and Differentiate

Extracellular Matrix Proteins

1. EASY Science Daily: Potential Therapy For Congenital Muscular Dystrophy
2. MID Science Daily: Molecule that Coordinates the Movement of Cells Identified
3. MID Description of research, Engler Lab, UC San Diego

Forces

1. EASY University of California: UC Berkeley bioengineer to receive NIH New Innovator Award
2. MID Phys.org: Small mechanical forces have big impact on embryonic stem cells
3. MID Science Daily: Modeling Cell Division: How A Cell Interacts With Its Microenvironment

Cell-cell interactions

1. MID Science Daily: Receptor Also Active Inside the Cell

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